REMARKS

I. Status of Claims

Currently, claims 1-10, 12-18, 21-29, and 40-52 are pending in this application. Claims 12, 14, 16-18, and 21-24 have been withdrawn from consideration by the Office as directed to non-elected inventions. Claims 1-10, 13, 15, 25-29, and 40-52 stand rejected.

By this amendment, Applicant proposes to amend independent claims 1, 3, 5, 7, and 9 by changing the upper end of the range for the high pH buffer from 14 to 12. Support for these amendments can be found throughout the specification, including, for example, at page 12, lines 17-20; page 29, lines 4-8, Figure 2, and pages 80-82.

Thus, the proposed amendment does not introduce new matter.

Applicant respectfully requests that the Examiner enter this Amendment under 37 C.F.R. § 1.116, placing the pending claims in condition for allowance or better form for appeal. Applicant submits that the proposed amendments do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner because the subject matter of amended claims 1, 3, 5, 7, and 9 has been previously examined in claims 42-46, which recite an upper pH range of 12. This Amendment should, therefore, allow for immediate action by the Examiner.

II. Rejection Under 35 U.S.C. §112, First Paragraph

The Office rejects claims 1-10, 13, 15, 25-29, 40, 49, and 50 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not enable one of skill in the art to make and use the invention commensurate in scope with the claimed invention. Final Office Action at page 9. The Office acknowledges that "the specification, while being enabling for a range of pH 9.3 to 11.8, does not reasonably provide enablement for a range greater than pH 12 to pH 14." *Id.* Although Applicant respectfully disagrees, in an effort to expedite prosecution, and not in acquiescence to the pending rejection, independent claims 1, 3, 5, 7, and 9[1] have been amended to recite that the high pH ranges from 9.3 to 12 (instead of 14), similar to claims 42-46 and 51-52, which recite that the high pH ranges from pH 9.5 to 12 and were not subject to this rejection. Accordingly, Applicant respectfully requests that the Office reconsider and withdraw this rejection.

III. Rejections Under 35 U.S.C. § 103

A. Wang

The Office maintains the rejection of claims 1-4, 7-11, 13, 15, 19, 25-30, and 40-46[2] under 35 U.S.C. § 103(a) as allegedly obvious over WO 01/082501 (*Wang*). Final Office Action at page 4. Applicant respectfully traverses this rejection.

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[1] The remaining claims under rejection depend directly from claims 1, 3, 5, 7, and 9.

[2] Applicant notes that claims 11 and 29 have been cancelled.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See* M.P.E.P. § 2143. Applicant submits that *Wang*, alone, or in combination with the state of the art, does not teach all of the elements of the rejected claims.

Wang does not teach the pH range of 9.3 to 12 (claims 1-4, 7-10, 13, 15, 25-29, 40, and 41) or 9.5 to 12 (claims 42-46). *Wang* teaches using a Pfu-Sso7d polymerase fusion with the standard reaction buffer for wild type Pfu polymerase, which contains 20 mM Tris-HCl (pH 8.8) as a buffering component. In addition, as noted by the Office, *Wang* teaches a buffer containing Tris HCl with a pH of 9.0 for the DyNAzyme EXT, which is a mixture of DyNAzyme II DNA polymerase and a proofreading enzyme. Final Office Action at page 4. The Office argues that it would have been obvious as a matter of routine optimization to increase the pH used with the Pfu-Sso7d fusion protein of *Wang* to 9.3 or 9.5. Office Action mailed 4 March 2008 at pages 5-6. For the reasons of record, Applicant asserts that it would not have been obvious to use the Pfu-Sso7d polymerase fusion of *Wang* at a pH of either 9.3-12 or 9.5 to 12.

The Federal Circuit has held that "a prima facie case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties." *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). Thus, an exception to the general rule exists when the difference between the prior art and the claimed range are such that one of skill in the art would not have expected them to have the same properties. That exception applies here. As established through the Borns

Declaration[3], one skilled in the art would *not* have expected that the reaction buffer in *Wang* would have the same properties if the pH were raised to 9.3 or 9.5. Specifically, one of skill in the art would have expected that increasing the pH of the reaction buffer disclosed in *Wang* to a pH of 9.3 or 9.5 would significantly impair the conditions for amplification with either the wild type Pfu DNA polymerase or the claimed Pfu-Sso7d fusion polymerase. Declaration at ¶ 16.

More specifically, Attachment B to the Declaration shows that although wild type Pfu DNA polymerase has optimal activity at pH 8.8, it loses this activity above pH 9, as acknowledged by the Office. Office Action mailed 4 March 2008 at page 3 ("[T]he declaration: (1) provides evidence only showing that a non-chimeric polymerase which is PFU Turbo loses activity above pH 8.8 (see Attachment B) . . . ."). The Declaration explains that *for the same reasons*, one of skill in the art would expect that a Pfu-Sso7d fusion polymerase containing a wild type Pfu DNA polymerase, such as the one disclosed in *Wang*, would similarly lose activity above pH 9. *See* Declaration at ¶ 16. Thus, one of skill in the art would not be motivated to increase the pH of the reaction buffer (pH 8.8) disclosed in Example 6.1 of *Wang* to a pH of 9.3 or 9.5 because he would expect that such a change would significantly impair the conditions for amplification with either the wild type Pfu DNA polymerase *or the Pfu-Sso7d fusion polymerase*. *See* Declaration at ¶ 16. Accordingly, contrary to the Office's assertions, and absent the teachings of the present specification, one of ordinary skill in the art having experience working with DNA polymerases would expect the differences between the conventional pH used for Pfu-based PCR in *Wang* (about 8.3 to 8.8) and the pH of the buffer

[3] *See* Attachment 1 to response filed 17 December 2007.

recited in the pending claims (9.3 to 12 or 9.5 to 12) to significantly impair the efficiency of PCR performance. *See* Declaration at ¶ 16.

In response, the Office cites Dietrich et al. (2002) ("*Dietrich*") as establishing that "it was known in the art that polymerases function at pH 9.5 and up to pH 10." Final Office Action at page 4. The Office further asserts that *Dietrich* "also support, as given below, that polymerase activity can be found over a broad pH range of pH 7 to pH 10 which is consistent with the teachings of Wang." *Id.* Thus, the Office concludes that "Applicant's opinion that one of ordinary skill in the art would not have expected the polymerase fusion of *Wang* to function at pH 9.5 is not supported by the teachings of the prior art." *Id.* at 4-5.

Applicant's response is that *Dietrich* is directed to a polymerase from *Pyroccocus abyssi* ("Pab"), whereas the claimed fusion protein comprises a *Pyrococcus furiosus* ("Pfu") DNA polymerase. It is improper for the Office to draw generalizations about DNA polymerases based on the biochemical properties of a single enzyme. This is particularly true here because Applicant has shown in the Borns Declaration that the Pfu DNA polymerase loses activity above pH 9. This is not disputed. Moreover, it should not be disputed that it is the biochemical properties of Pfu DNA polymerase—not the Pab DNA polymerase—that are relevant to the presently claimed invention and the question of whether one of skill in the art would have been motivated to increase the pH of the Pfu-Sso7d polymerase fusion protein buffer to 9.3 or 9.5.

Furthermore, there are no data supporting the statements in *Dietrich* that

> Pab was more active at pH 9 in glycine-NaOH buffer and pH 9.5 in CAPS buffer. Using Tris-HCl buffer, Pab retained more than 80% of

> its optimal activity between pH range 7-10 and appeared to possess an extended range of DNA polymerizing activity.

Dietrich at 92, first column. Instead, the only pH-dependency data reveal that the Pab DNA polymerase dramatically loses activity above the optimal pH of 9.0. Specifically, a review of the reference[4] allegedly supporting the statements in *Dietrich* about pH dependency demonstrates that while the Pab DNA polymerase ("Pol I") has an optimum pH of 8.5-9.0, the enzyme exhibits a marked decrease in activity when the pH rises above 9.0 and essentially loses activity altogether at pH 9.5. *Gueguen* at p. 5961 (Abstract) and p. 5965 (Fig. 4A). This is also consistent with the properties of the Pfu DNA polymerase, which has optimal activity at pH 8.8 but loses activity above pH 9. *See* Declaration at ¶ 13.

"In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983) . . . ." M.P.E.P. § 2141.02. Before Applicant's discovery, there was a perceived need in the art to use a pH buffer below pH 9 when using a Pfu polymerase (either as a non-fusion or fusion polypeptide). Applicant, on the other hand, unexpectedly found that raising the pH above 9 actually enhances rather than impairs the PCR performance efficiency of a Pfu fusion polymerase. Because that insight was contrary to the expectations and understandings of the art, it would not have been obvious to modify the teachings of *Wang* to

[4] Gueguen et al., Eur. J. Biochem. 268, 5961-69 (2001) ("*Gueguen*"); *see* Attachment A.

arrive at the methods of the presently claimed invention reciting a high pH of 9.3 to 12 or 9.5 to 12. *See Schenck*, 713 F.2d at 785, 218 USPQ at 700 ("Because that insight was contrary to the understandings and expectations of the art, the structure effectuating it would not have been obvious to those skilled in the art."). Accordingly, for the reasons of record, the Borns Declaration provides persuasive evidence showing that it would not be *prima facie* obvious to "optimize" the buffer used in *Wang* by increasing the pH to 9.3 or 9.5. In fact, the art teaches away from doing just that.

Accordingly, Applicant submits that *Wang* fails to teach or suggest all elements of claims 1-4, 7-10, 13, 15, 25-29, and 40-46 and, thus, does not render those claims obvious. For at least this reason, Applicant requests that the Office reconsider and withdraw the rejection of these claims as unpatentable over *Wang*.

B. Wang in Combination with Sanger

The Office maintains the rejection of claims 5 and 6 under 35 U.S.C. § 103(a) as allegedly obvious over *Wang* in combination with *Sanger*. Final Office Action at page 5. Applicant respectfully traverses this rejection.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See* M.P.E.P. § 2142. Applicant submits that the combined teachings of the cited references do not teach all of the elements of the rejected claims. For the reasons discussed above, *Wang* fails to teach or suggest a pH from 9.3

to 12, as recited in claims 5 and 6. *Sanger* also fails to teach or suggest this element of the claims and thus fails to remedy the deficiencies of *Wang*.

Accordingly, Applicant submits that the combined teachings of *Wang* and *Sanger* fail to teach or suggest all elements of claims 5 and 6 and, thus, do not render those claims obvious. For at least this reason, Applicant requests that the Office reconsider and withdraw the rejection of claims 5 and 6 as unpatentable over the combination of these references.

C. Wang

The Office rejects claims 47 and 48[5] under 35 U.S.C. § 103(a) as allegedly obvious over *Wang*. Final Office Action at page 5. Applicant respectfully traverses this rejection for the reasons of record. Namely, *Wang* fails to teach or suggest a pH from 9.5 to 12, as recited in claims 47 and 48, which depend directly or indirectly from claim 42. For at least this reason, Applicant requests that the Office reconsider and withdraw the rejection of claims 47 and 48 as unpatentable over *Wang*.

Applicant traverses this rejection as to claims 47 and 48 for the additional reason that *Wang* fails to teach or suggest a blend comprising a polymerase fusion and a second DNA polymerase, let alone a blend where the second DNA polymerase is a Pfu DNA polymerase. Although *Wang* teaches mixtures of non-fusion polymerases, it also teaches that those mixtures

[5] Although the rejection lists claims 49-52, only claims 47 and 48 are discussed. Thus, Applicant understands that this rejection pertains to claims 47 and 48—not claims 49-52.

require one proofreading polymerase and one non-proofreading polymerase. Specifically, *Wang* states:

> Currently, PCR amplification of long DNA fragments requires the use of an enzyme mixture containing both a non-proofreading polymerase (e.g. Taq or DyNAzyme II) and a small amount of proofreading polymerase *(e.g.* Pfu or Deep Vent). We have compared a single fusion enzyme, Pfu-Sso7d, to one of the high performance, long PCR enzymes DyNAzyme EXT (from Finnzymes) in long PCR, and demonstrated that Pfu-Sso7d outperforms DyNAzyme EXT, especially with limited extension time.

Wang, pages 39-40. Furthermore, *Wang* teaches that the polymerase fusion outperforms the non-fusion polymerase mixture.

Thus, as to claims 47 and 48, *Wang* teaches away from adding a second DNA polymerase to a polymerase fusion because the polymerase fusion of *Wang* outperforms the state of the art polymerase mixtures and was intended as a substitute for such mixtures. The Office asserts that "it is expected that a blend of fusion polymerase Pfu-Sso7d and Pfu polymerase would have functioned in the claimed method, as *Wang* teaches both polymerases function at high pH (See example 6-1)." Final Office Action at page 6. Applicant's response is that *Wang* does not teach that either the Pfu polymerase or the Pfu-Sso7d polymerase fusion functions at a pH above 9. Moreover, the evidence of record shows that Pfu loses its activity at a pH above 9 and that one of skill in the art, as of the filing date of Applicant's application, would have expected a Pfu-Sso7d polymerase fusion to similarly loses its activity at a pH above 9.

Wang further teaches away from claim 48, which recites that the second DNA polymerase is Pfu, because *Wang* teaches that the mixture requires a proofreading polymerase

and a non-proofreading polymerase. The blend in claim 48, on the other hand, comprises two proofreading polymerases, a Pfu-Sso7d polymerase fusion and Pfu. *Wang* does not teach or suggest using two proofreading polymerases in a mixture.

Accordingly, for these additional reasons, Applicant requests that the Office reconsider and withdraw the rejection of claims 47 and 48 as unpatentable over *Wang*.

D. Wang in Combination with Dietrich

The Office rejects claims 49-52 under 35 U.S.C. § 103(a) as allegedly obvious over *Wang* in view of *Dietrich*. Final Office Action at page 7. Applicant respectfully traverses this rejection.

The Office acknowledges that "Wang does not specifically teach using the Pfu-Sso7d fusion polymerase protein at the pH range of 9.5 to 12." *Id.* The Office, however, asserts that

> it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods for a modified polymerase of Wang by using a higher pH as suggested by Dietrich et al. with a reasonable expectation of success. The motivation to do so is provided by Dietrich et al. who teach recombinant modified polymerases can have more activity at pH 9.5 and can retain more than 80% of optimal activity over a broad pH range of 7 to 10.

Id. at 8.

As discussed above, it is improper for the Office to extrapolate a general teaching about DNA polymerases from a specific reference about a *Pab* DNA polymerase, particularly here, where the evidence of record shows that *Pfu* DNA polymerase loses its activity above pH 9.

Dietrich cannot provide one of skill in the art with a reasonable expectation of success when the evidence of record shows that Pfu loses its activity above pH 9 and that one of skill in the art would similarly expect a pH above 9 to significantly impair the conditions for amplification when using a fusion protein comprising Pfu. Declaration, ¶ 16. *Dietrich*, therefore, is far less relevant, if relevant at all, than the evidence of record regarding Pfu DNA polymerase and fusion proteins comprising the same. Accordingly, in view of the totality of the evidence, *Dietrich* does not provide the motivation for raising the pH of the buffer used with *Wang*'s Pfu-Sso7d fusion polymerase to 9.3 or 9.5.

The Office further asserts that

> it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the claimed pH of 9.5 and above as used by the applicant or in the range of pH 9.0 as used by Wang since these differences in pH would not be expected to greatly alter the conditions for amplification. One of ordinary skill in the art would have not expected that the activity of a DNA polymerase fusion would be completely lost at pH 9.5 when it was functional at pH 9.0.

Id.

Applicant's response is that based on the evidence of record, one of skill in the art would have expected the differences in the pH of *Wang* and the claimed pH to significantly impair the conditions for amplification. As discussed above, the Borns Declaration establishes that one of skill in the art would have expected that increasing the pH of the reaction buffer in Example 6-1 of *Wang* from 8.8 to above 9 would significantly impair the conditions for amplification with *Wang*'s Pfu-Sso7d fusion polymerase, just as it did for the wild type Pfu polymerase. Declaration, ¶ 16. The Office attempts to rebut this evidence by citing *Dietrich*, but the

statements in *Dietrich* about the Pab DNA polymerase maintaining significant activity at pH 9.5-10 does not refute the evidence of record showing that the Pfu DNA polymerase loses its activity above pH 9 and has little to no activity at pH 9.5. Furthermore, *Gueguen*, which discloses pH dependency studies for Pab DNA polymerase and is cited in *Dietrich*, actually shows that Pab DNA polymerase does not maintain significant activity at pH 9.5-10 but rather undergoes a drastic reduction in activity at pH greater than 9, essentially losing activity altogether at pH 9.5.

Finally, the Office asserts:

> Routine optimization is not considered inventive and no evidence has been presented that the selection of pH 9.5 was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art of pH 9.0. As noted, a skilled artisan would expect a pH of 9.0 to have nearly identical properties in the amplification of nucleic acids. Thus, an ordinary practitioner would have recognized that the results could be adjusted to maximize the desired results especially in view of the teachings of Dietrich et al. as given above.

Final Office Action at page 9.

As discussed above, selection of a pH of 9.3 to 12 or 9.5 to 12 was not routine optimization because one of skill in the art would have expected the differences between the conventional pH used for Pfu-based PCR in *Wang* (about 8.3 to 8.8) and the pH of the buffer recited in the claims (9.3 to 12 or 9.5 to 12) to significantly impair the efficiency of PCR performance. *See* Declaration at ¶ 16.

Another exception to the general rule that "'the discovery of an optimum value of a variable in a known process is normally obvious,' . . . is where the parameter optimized was not

recognized in the prior art as one that would affect the results." *Ex parte Whalen II*, No. 2007-4423, 2008 WL 2957928, *8 (B.P.A.I. July 23, 2008)[6] (citations omitted). In *Whalen II*, the Board found that "the Examiner has not pointed to any teaching in the cited references, or provided any explanation based on scientific reasoning, that would support the conclusion that those skilled in the art would have considered it obvious to 'optimize' the prior art compositions by increasing their viscosity to the level recited in the claims." *Id.* In fact, the evidence of record in *Whalen II* established that low viscosity was a desired property of the prior art compositions. *Id.*

Similarly, in this application, the Office has not provided any evidence or any explanation based on scientific reasoning that one of skill in the art would have considered it obvious to optimize the Pfu-Sso7d fusion polymerase compositions of *Wang* by increasing the pH above 9, and in particular to the claimed range of 9.3 to 12 or 9.5 to 12. Rather, the evidence of record establishes that a pH below 9 was a desired property for compositions comprising Pfu or a Pfu-Sso7d fusion polymerase. In fact, the skilled artisan would have expected that raising the pH of the reaction buffer in *Wang* to 9.3 or higher would impair—not enhance—the efficiency of the disclosed Pfu-Sso7d fusion polymerase. Declaration at ¶¶ 16-18. Also, it appears that in Example 6.1, *Wang* used a commercially available reaction buffer for Pfu. Declaration at ¶ 15. One of ordinary skill in the art would not have been motivated to increase the pH of this reaction buffer as a matter of routine optimization for the additional reason that, as a commercial product, the reaction buffer would have already been optimized. *See* Declaration

[6] *See* Attachment B for a copy of this precedential opinion.

at ¶ 16. As discussed above, the Office's citation of *Dietrich* for the general principle that polymerases function at pH 9.5 and up to pH 10 is misplaced and does not address the evidence of record showing that it was known in the art that the Pfu polymerase loses its activity above pH 9. Thus, the art teaches away from increasing the pH buffer of *Wang* above 9 based on the expectation and understanding that doing so would impair the efficiency of *Wang's* Pfu-based fusion protein. *Whalen II*, 2008 WL 2957928, at *9 ("when the prior art teaches away from the claimed solution as presented here . . ., obviousness cannot be proven merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition.").

For at least this reason, Applicant requests that the Office reconsider and withdraw the rejection of claims 49-52 as unpatentable over *Wang* in combination with *Dietrich*.

IV. Conclusion

Applicant believes that this application is in condition for allowance. If the Office believes anything further is required in order to place this application in even better condition for allowance, Applicant requests that the undersigned representative be contacted at the number listed below to discuss remaining issues.

Please grant any extensions of time required to enter this paper and charge any additional required fees to Deposit Account No. 50-3740.

Respectfully submitted,
Michael BORNS

Date: 8 December 2008

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Attachment A
Gueguen et al., Eur. J. Biochem. 268, 5961-69 (2001).

Attachment B
Copy *Ex parte Whalen II*, 2008 WL 2957928 (B.P.A.I. July 23, 2008).